Asymmetrical aortic root aneurism in patient with Filamin A mutation

ASYMMETRICAL AORTIC ROOT ANEURISM IN PATIENT WITH FILAMIN A MUTATION

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ABSTRACT

Filamin A gene mutations might result in brain, blood vessels, heart and connective tissue disorders. A miscellany of cardiovascular abnormalities could be present. We report the case of a young woman with cerebral Periventricular Nodular Heterotopia, due to Filamin A mutation and asymmetrical aneurysm of the non-coronary Valsalva sinus.

INTRODUCTION

Filamin A (FLNA) is an Actin-binding protein encoded by FLNA gene, Xq28[1]. FLNA is a widely expressed cytosolic protein, that regulates cytoskeleton by serving as a scaffold for actin filaments and interacting with adhesion-molecules, thereby playing a key role both in architectural and signaling cell functions[2,3,4]. The entirety of its functions is not fully understood, but it is most probably involved also in development of blood cells, angiogenesis and cellular migration during the embryonic period[5,6].

Cardiovascular abnormalities typically associated to FLNA mutations are various, including persistent ductus arteriosus, perimembranous ventricular septal defect clinical features resembling Ehlers-Danlos syndromes as well as arterial aneurysms and a form of non-syndromic mitral valve prolapse (MVP). Sometimes, neurological manifestations embody the clue to diagnosis. Common neurological symptoms are seizures and dyslexia[7]. In patients with PNH due to FLNA mutation, cardiovascular symptoms may dominate patient's history[8]. The exact prevalence of cardiovascular involvement in patients with X-linked FLNA mutation and PNH is largely unknown and probably

underestimated. We report the case of a young lady with diagnosis of PNH and incidental finding of aortic aneurysm of ascending aorta, for which she underwent valve-sparing aortic root replacement.

CASE REPORT

A 28 years old woman was admitted at the Neurology Unit with recurrent short (about 10 seconds) episodes of aphasia. Given the suspicious of seizures, a brain MRI was performed revealing a megacisterna magna and diffuse bilateral subependimal nodular heterotopia. A diagnosis was made: episodes of seizure in cortical heterotopia. FLNA genetic analysis revealed a non-sense mutation due to a nucleotide substitution at c.4294C>T resulting in an early truncated protein at the l432 aminoacid. Afterwards, cardiovascular screening was advised. The patient was evaluated through transthoracic echocardiography and cardiac MRI. The echo showed a huge aneurysm of the aortic root with dilatation of the ascending aorta above the sinotubular junction, associated with moderate aortic regurgitation in a tricuspid aortic valve. The leaflets showed only mild thickening and the regurgitation jet was central. The cardiac MRI confirmed echo's findings, particularly the asymmetric aortic root aneurysm involving especially the non-coronary sinus of Valsalva, which developed caudally toward the right atrial roof reaching a maximum diameter of 61 mm. The ascending aorta and the proximal arch measured 43 mm and 32 mm respectively. The aortic arch was noteworthy because the left common carotid artery emerged from the brachiocephalic trunk, a condition known as "bovine arch". The remaining aortic segments were normal (Fig. 1). Familiar history of seizures, cardiovascular disorders and genetic analysis of the relatives were negative.

Aortic root replacement with reimplantation of the aortic valve and coronary arteries was performed, using a 28 mm Vascutek Valsalva conduit[9]. Aortic cusps were holdup and the three free edges plicated with a 6/0 polytetrafluoroethylene (PTFE) running suture.

The pathology examination was carried out on two aortic specimens, one from the ascending tract (5 cm long) and a smaller one from the non-coronary sinus (1.3 cm long). At macroscopic examination, the aortic wall was globally thinned, being this finding particularly evident in the non-coronary sinus specimen and in the proximal tract of the ascending segment.

Histology showed differentiated findings. The specimen from the non-coronary sinus was diffusely thinned, ranging from 0.2 mm to 1 mm in wall thickness (Fig. 2A), revealing a subverted parietal structure (Fig. 2B) along with severe medial alterations. Smooth muscle cells (SMCs) showed marked disarrangement with altered orientation (Fig. 2C) and dimensional variability associated with coarse collagen bands and replacement fibrosis around nodules of SMCs (Fig. 2D). The elastic component was extremely scarce and, in some areas, it was constituted of fragmented lamellae.

The specimen from the ascending aorta (ranging from 0.7 mm to 2 mm in thickness), in the context of a preserved lamellar structure, showed common medial degenerative damage including focal laminar medial collapse, intralamellar and translamellar collagen increase, multifocal elastic fibre fragmentation associated with intralamellar and translamellar mucoid matrix deposition/pooling and SMCs loss (Fig. 3). These alterations were more evident in its proximal tract.

After surgery, the patient spent one day in the Intensive Care Unit. The post-operative course was uneventful, and she was discharged home 8 days after surgery. The post-operative echocardiogram showed no signs of residual aortic regurgitation.

DISCUSSION

It is well known that PNH might be frequently accompanied by FLNA mutation and cardiovascular disease. One of the largest studies on PNH presented by Parrini et al[10], was able to assess the extreme heterogeneity of PNH. Based on comparison of clinical and MRI findings in 182 patients, they identified 15 subgroups: the largest group (98 patients, 54%), defined as Classical Bilateral PNH, may include our case. Mutated FLNA was found in 49% of the tested patients (72 out of 98) with Classical Bilateral PNH. Moreover, the authors reported a high prevalence of cardiovascular abnormalities -such as aortic valve regurgitation and patent ductus arteriosus- among this subgroup.

Chen et al[11] partially confirmed these findings, reporting perimembranous ventricular defect, patent ductus arteriosus and mitral valve prolapse among cardiovascular lesions FLNA related. The authors also underlined the link between FLNA and asymmetric aortic aneurysms leaning to sudden rupture, with preferential involvement of RCC and NCC. This is due to the origin of the distal left ventricular outflow tract from neural crest cells.

Cardiac symptoms in patients with PNH may precede neurological manifestations. De Wit et al[12] reported a combination of cardiac disease and bilateral PNH in 5 patients out of 6 with FLNA mutation; interestingly, in 4 cases patients presented to a cardiologist before or at the time of their neurological workup. Cardiac findings showed, once again, wide heterogeneity, ranging from a stable mild aortic dysfunction to severe aortic regurgitation with dilated heart, dilated aortic root, infrarenal aortic aneurysm and bilateral fusiform carotid aneurysms.

The heterogeneity of cardiac involvement in patients with PNH was confirmed by Reinstein et al[13]. In a population of 11 individuals, the authors report how arterial disease can be diffused, affecting both systemic and pulmonary circulations.

A clinical report published by Jefferies et al described the presence of patent foramen ovale, dysplasia of the pulmonary valve and cleft of the mitral valve in a 18-month-old girl with PNH, further broadening the range of cardiac abnormalities associated to this condition[14].

A possible explanation for the vascular impairment observed in patients with PNH was suggested by Feng Y et al[15]. Throughout their analysis on FLNA-knock out mice they underlined the key role of FLNA not only in cellular migration but also in adherent junctions, which are essential for the organization of vessels during angiogenesis. The loss of FLNA in their model resulted in abnormal adherent junctions leading to endothelial integrity deficiency and vascular disorganization. Moreover, Chen et al[16] showed how FLNA levels in aortic specimens after acute dissection are decreased, subsequently increasing metalloproteinases activity. To our knowledge, aortic root aneurysm with aortic valve regurgitation in patients with FLNA gene variant has been reported two times only[17,18]; on both occasions, a valve sparing aortic root replacement (David procedure) was performed. Only one between these two reports described the histological abnormalities in the aortic specimen of a patient carrying a FLNA mutation. The striking aspect of pathology examination was the subverted architecture with extreme thinning of the tunica media of the non-coronary sinus, which revealed severe structural disarrangement of the muscular and collagenous components, associated with relevant deficiency of elastic fibres. The ascending aorta showed degenerative medial alterations usually found in several genetic aorthopathies.

The described structural disarrangement of the aortic media might be related to FLNA involvement in cell-to-cell interactions, regulation of cytoskeleton proteins and secretion of metalloproteinases, all essential elements in architectural organization of vessel walls.

FLNA gene mutations have not been frequently described in Cardiac surgery, despite the fragility of the connective tissues just observed in the aortic root. FLNA gene mutations appear to be associated with severe form of degenerative changes of vessels wall. Additional surgical care is needed, and patients have to remain under medical surveillance with periodical images of the aortic root, because of the severe and probably underestimanted form of aorthopaty just discussed.

In conclusion, in patients carrying a FLNA mutation, cardiac evaluation is advised. It should be comprehensive, including imaging of the great arteries.

CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS STATEMENT

The authors confirm that the consent for submission and publication of this case report including images and associated text has been obtained from the patient.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the manuscript and read and ap-proved the final version of the manuscript.

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FIGURE LEGENDS

Figure 1

Magnetic Resonance (Black and bright blood morphologic and Whole-heart volumetric sequences) showing in A and B pre-operative aortic root dilatation with Valsalva sinuses measuring 45 x 63 mm in diameter due to a significant aneurysm of the non-coronary sinus. Maximum diameter of the ascending aorta measured 43 mm and the proximal tract of the aortic arch measured 32 mm in diameter.

Figure 2

Non coronary sinus sample. A: slide of two specimens of the non coronary sinus aortic wall showing severe thinning with a minimum thickness of 0.2 mm (inset) (Azan-Mallory trichrome). B: The aortic wall shows a complete architectural subversion of the medial layer with disoriented muscular bundles (Azan-Mallory trichrome; original magnification 100x). C: immunohistochemical stain with a smooth muscle cell actin antibody highlights medial smooth muscle cells disarrangement (original magnification 250x). D: coarse collagen bands were found in the tunica media around the muscular component (arrow) (Azan-Mallory trichrome; original magnification 200x).

Figure 3

The ascending aorta specimen revealed various degenerative alterations in a moderate degree: focal laminar medial collapse (arrow) (A; Weigert-Van Gieson, original magnification 250x); intralamellar and translamellar collagen increase, emphasized in blue with Azan-Mallory trichrome (B, original magnification 250x); marked elastic fibres fragmentation (arrow) (C, Weigert-Van Gieson, original magnification 200x); translamellar mucoid matrix deposition (asterisk) (D, Haematoxylin-Eosin, original magnification 250x).